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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/875,076	06/06/2001	Chen W. Liaw	AREN-0239	6379
35133	7590	05/19/2006	EXAMINER	
COZEN O'CONNOR, P.C. 1900 MARKET STREET PHILADELPHIA, PA 19103-3508			MERTZ, PREMA MARIA	
			ART UNIT	PAPER NUMBER
			1646	

DATE MAILED: 05/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/875,076	Applicant(s) LIAW ET AL.	
	Examiner Prema M. Mertz	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 April 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 77-101 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 77-101 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>4/18/2006</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/13/2006 has been entered.
2. Claims 77-101 are pending and under consideration.
3. Receipt of applicant's arguments and amendments filed on 4/13/2006 is acknowledged.
4. Applicant's arguments filed on 4/13/2006 have been fully considered and were non-persuasive. The issue remaining is restated below.
5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim rejections-35 USC § 101

6. Claims 77-101 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial utility or a well established utility.

This rejection is maintained for reasons of record set forth at pages 3-6, of the previous Office action (3/21/03), pages 2-8 of the previous Office action (3/18/05), and pages 2-8 of the previous Office action (10/13/05).

Applicants argue that the utility rejection can be maintained only if the totality of the record shows the utility is not specific, substantial and credible. Applicants also argue that there is no requirement for Applicants to disclose compounds that specifically activate or inhibit hARE-2 or diseases associated with hARE-2 dysfunction and because a well-established

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utility satisfies the requirement under 35 U.S.C. 101, these can come from the knowledge in the art, if needed. In addition Applicants argue that the totality of the record clearly indicates a well-established utility, namely the use of hARE-2 for treating disorders of the substantia nigra, such as Parkinson's disease. However, contrary to Applicants arguments, Applicants have failed to provide a nexus between expression of the instant mRNA encoding hARE-2 protein and any diseases of the substantia nigra. Just because mRNA encoding the hARE-2 protein is expressed at its highest levels in the substantia nigra (see page 27, Table C), does not provide a nexus for using hARE-2 protein for treating disorders of the substantia nigra, such as conditions like Parkinson's disease. In fact, Applicants have failed to demonstrate any type of differential expression of the instant protein in normal substantia nigra tissue and in disorders of the substantia nigra. In fact, it is equally possible that expression of the hARE-2 protein may have to be inhibited in disorders of the substantia nigra. Significant further research would have to be required of the skilled artisan to characterize the polypeptide of SEQ ID NO:20 to determine its biological activities or other specific utilities.

The instant protein of SEQ ID NO:20 has 53% identity to GPR27. Ji et al. (1998) review the functional diversity among the structurally related G protein-coupled receptors (see page 17299, column 1, third paragraph, lines 22-23). In view of the fact that structural similarity cannot accurately predict functional similarity, there is no well-established utility for newly isolated hARE-2. Furthermore, Applicants argue that GPCRs affect the level of cAMP or IP3 in a cell (see page 12, line 2 to page 13, line 16) and also cite the supporting Graph 1 filed September 19, 2003 in this regard. However, contrary to Applicants arguments, what is disclosed on pages 12-13 of the instant specification is general teachings of regarding all GPCRs.

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With respect to Graph 1 (9/19/2003), the Graph demonstrates a reduction of the level of intracellular cAMP in cells transfected with hARE-2 but it is unclear from the instant specification whether the instant hARE-2 protein functions as a GPCR. The issue here is not that hARE-2 is a GPCR but that an analysis of the instant specification does not meet the requirements of 35 USC 101 for a specific and substantial asserted utility or a well-established utility. An asserted utility must meet the three-pronged test of being credible, specific and substantial. The utilities for the proteins recited in the instant specification are generic utilities that fail to satisfy all three prongs. In the instant case, GPCRs are structurally similar compounds with diverse functions. The skilled artisan would have to conduct significant further research to determine the particular functions of the instant hARE-2 protein in order to identify a specific and substantial utility for the new hARE-2 protein. Therefore, the asserted utilities in the instant specification are not specific or substantial.

Applicants argue that the fact that hARE-2 influences the viability of neurons in the substantia nigra is supported by the data previously submitted in Graph 1. However, contrary to Applicants arguments, there is no doubt that hARE-2 reduces the level of intracellular cAMP. However, the specification "as originally filed" merely discloses that hARE-2 is present in substantia nigra. It would have taken significant research to determine the role of hARE-2 in substantia nigra and the role of hARE-2 in a disease such as Parkinson's disease and only once these roles were determined, then hARE-2 could be used to screen for compounds to treat the disease. Therefore, one of skill in the art, as of the filing of the instant application, would not have discerned the role of hARE-2, because there is no disclosure suggesting what type of role is played by hARE-2.

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Applicants argue that the importance of hARE-2 as a GPCR is that GPCRS, such as hARE-2, are known to affect intracellular levels of cAMP or IP3. The fact that hARE-2 has such an effect is exemplified in the previously submitted Graph 1, thus supporting the utility. However, contrary to Applicants arguments, at the time of the filing of the instant application there was no showing that hARE-2 constitutively couples to Gi. This information was disclosed in arguments submitted four years after the earliest priority date of the instant application. Therefore, it is evident that further experimentation was required to determine the biological function of hARE-2. There is no showing in the instant disclosure of the specific role of hARE-2 i.e. reduction in intracellular cAMP levels. The instant specification only discloses general functional activities of GPCRs which are applicable to a wide variety of G-protein coupled receptor family members but does not disclose any specific activity associated with the claimed hARE-2 that provides support for either a specific and substantial asserted utility as a well established utility under 35 USC 101.

Applicants also argue that those of skill in the art would recognize hARE-2 is useful to screen for compounds for promoting the viability of neurons in the substantia nigra and to treat Parkinson's disease based on the effect hARE-2 and inverse agonists, agonists and partial agonists thereof have on the level of intracellular cAMP or IP3 as a GPCR in the substantia nigra. Applicants also argue that hARE-2's affect on these levels is confirmed by Applicants' previously submitted Graph 1. However, contrary to Applicants arguments, as stated by the Examiner previously, the data submitted in Graph I was not disclosed in the application as filed but submitted four years after the earliest priority date of the instant application. In addition, at the time of filing of the instant application, treating or treating for compounds that interact with

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hARE-2, which may be implicated in an unspecified condition would require or constitute carrying out further research to identify or reasonably confirm a “real world” context of use. Since neither the instant specification nor the art of record disclose any activities or properties that would constitute a “real world” context of use for the claimed polynucleotide encoding hARE-2, further experimentation is necessary to attribute a utility to the claimed polynucleotide encoding hARE-2.

Applicants argue that in addition to the utility of treating Parkinson's disease, those of skill in the art would also recognize the well-established utility in diagnosing Parkinson's. Those of skill in the art would have known at the time of filing that Parkinson's disease is caused by a loss of neurons in the substantia nigra and Applicants' disclosure indicates that hARE-2 is selectively expressed in the substantia nigra. However, contrary to Applicants arguments, with regard to diagnosis of disease, in order for a polynucleotide or protein to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polypeptide and a disease or disorder. The presence of a polynucleotide in the substantia nigra is not sufficient for establishing a utility in diagnosis of a disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed cDNA or protein and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in e.g. cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased

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tissue compared to normal tissue (i.e. over expression). Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the polynucleotide or the ~~claimed~~ polypeptide that is encoded thereby and any disease or disorder and the lack of any correlation between the polynucleotide or the encoded polypeptide with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself.

Furthermore, the rejection is based on the failure to disclose sufficient properties of the protein and/or polynucleotide to support an inference of utility. hARE-2 belongs to a family of proteins in which the members have divergent functions. Assignment to this family does not support an inference of utility because the members are not known to share a common utility. There are some protein families for which assignment of a new protein in that family would convey a specific, substantial and credible utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family.

The diversity of the biochemical function and the wide range of regulatory pathways involving GTP-binding proteins are well known in the art. Without some common biological activity for the family members, a new member would not have a specific, substantial, or credible utility when relying only on the fact that it has structural similarity to the other family members. The members of the family have different biological activities, which may be related to tissue distribution but there is no evidence that the claimed compounds share any one of

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diverse number of activities. That is, no activity is known to be common to all members. To argue that all the members can be used for diagnosis of Parkinson's disease is to argue a general, nonspecific utility that would apply to virtually every member of the family, contrary to the evidence.

Furthermore, any compound could be considered as a regulator or modulator of tissue in that any compound, if administered in the proper amount, will stimulate or inhibit tissue. For example, salt, ethanol, and water are all compounds which will kill cells if administered in a great enough amount, and which would stimulate cells from which these compounds had been withheld, therefore, they could be considered regulators or modulators of tissue. However, use of these compounds for the modulation of tissue would not be considered a specific and substantial utility unless there was some disclosure of, for example, a specific and particular combination of compound/composition and application of such in some particular environment of use. Further, the specification does not disclose the significance of any test results, nor is there any evidence that the significance was known as of the filing date. From the instant disclosure, if the expression of the claimed hARE-2, increases, is this a positive or negative outcome? The disclosure is insufficient to evaluate the results of the test in any meaningful manner.

Without knowing a biological significance of the claimed polynucleotide, one of ordinary skill in the art would not know how to use the claimed invention in its currently available form in a credible real world manner based on the diversity of biological activities possessed by GTP-binding proteins. Contrast *Brenner*, 148 USPQ at 694 (despite similarity with adjacent homologue, there was insufficient likelihood that the steroid would have similar tumor-inhibiting characteristics), with *In re Folkers*, 145 USPQ 390, 393 (CCPA 1965) (some uses can be

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immediately inferred from a recital of certain properties) or *In re Brana*, 34 USPQ 1436, 1441 (Fed. Cir. 1995) (evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility, here, an implicit assertion of a tumor target was sufficiently specific to satisfy the threshold utility requirement).

Applicants argue that the specification states that hARE-2 is a GPCR in the substantia nigra and consequently affects the intracellular levels of cAMP or IP3 and Graph I of 9/19/2003, merely confirms these assertions. However, contrary to Applicants arguments, in all cases, a practical utility of an invention may be derived from belonging to a broad class of inventions. The requirement in any particular case, however, is that practical utility can be inferred if each and every member of the broad class possesses a common utility. The question in the instant application is whether the members of the family of proteins to which the claimed invention is structurally related have, individually, a specific, substantial and credible or well-established utility. Applicant has failed to show by a preponderance of the evidence, in enough detail, with respect to the described hARE-2, has any substantial use. The record shows that the GTP-binding protein family is diverse, and has such a broad definition, that a common utility cannot be defined. Moreover, the evidence of record is inadequate to determine the diseases or drugs for which the compounds would be useful. In *Brenner*, the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPQ at 690. Here, there is no evidence that the claimed cDNA, plasmid containing said cDNA and host cell containing said plasmid have any utility. One of skill in the art based on the disclosure of the instant invention would not have made the nexus between a

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modulator of hARE-2 and the modulator being useful to treat Parkinson's disease. There is absolutely no nexus in the instant disclosure between modulators of hARE-2 and treatment of Parkinson's disease and no nexus between using the claimed polynucleotide encoding hARE-2 and loss of neurons in a method for diagnosing Parkinson's disease because Applicants have failed to show differential expression of the claimed polynucleotide encoding hARE-2 in normal substantia nigra tissue and in the substantia nigra of patients with Parkinson's disease. Further with the exception of a few house keeping genes, all polypeptides/polynucleotides have a tissue specific pattern of expression. Thus, the asserted utility is not specific to hARE-2.

Claim rejections-35 USC § 112, first paragraph

7. Claims 77-101 are also rejected under 35 U.S.C. 112, first paragraph.

This rejection is maintained for reasons of record set forth at pages 3-6, of the previous Office action (3/21/03), pages 2-8 of the previous Office action (3/18/05), and pages 2-8 of the previous Office action (10/13/05).

Specifically, since the claimed invention is not supported by either a specific, substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

Claims 77-101 are rejected.

No claim is allowed.

Advisory Information

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835.

Official papers filed by fax should be directed to (571) 273-8300. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Information regarding the status of an application may be obtained from the Patent application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Prema Mertz

Prema Mertz Ph.D., J.D.

Primary Examiner

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May 11, 2006